Original Study

High-dose Thiotepa, Busulfan, Cyclophosphamide, and Autologous Stem Cell Transplantation as Upfront Consolidation for Systemic Non-Hodgkin Lymphoma With Synchronous Central Nervous System Involvement

David Qualls,[1] Andrew Sullivan,[2] Shuli Li,[3] Andrew M. Brunner,[4] Kerry Collier,[5] Ephraim Hochberg,[6] Philippe Armand,[7] Tracy T. Batchelor,[8] Yi-Bin Chen,[5] Zachariah DeFilipp[5]

Abstract

Systemic non-Hodgkin lymphoma with synchronous central nervous system involvement traditionally carries a poor prognosis. We found encouraging results with the use of high-dose chemotherapy and autologous stem cell transplantation as consolidation for patients in first complete remission. Central nervous system-directed conditioning with a thiotepa-based regimen might reduce the incidence of relapse and improve the outcomes in this population.

Introduction: Synchronous involvement of the central nervous system (CNS) at the diagnosis of systemic non-Hodgkin lymphoma (NHL) is associated with an increased risk for relapse despite complete remission to initial therapy. High-dose chemotherapy with a CNS-directed conditioning regimen followed by autologous stem cell transplantation (ASCT) holds promise as a consolidative approach. **Patients and Methods:** We conducted a retrospective analysis of all patients with systemic B-cell NHL and synchronous CNS involvement who received upfront consolidation with high-dose chemotherapy with thiotepa, busulfan, cyclophosphamide, and ASCT while in first complete remission between July 2008 and June 2016 at 2 partner academic institutions. **Results:** Twenty patients were identified through the transplant database. The median age at diagnosis was 53 years (range, 37-65 years). The majority had diffuse large B-cell lymphoma histology (n = 17; 85%). The sites of CNS involvement were parenchymal (n = 12; 60%) and leptomeningeal disease (n = 9; 45%). All patients received systemic and CNS-directed therapy prior to transplant, with the most common approaches being R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone) (n = 13; 65%) and high-dose intravenous methotrexate (n = 16; 80%), respectively. With a median follow up of 4.4 years after ASCT (range, 2 months-8.5 years), the Kaplan-Meier estimates of 4-year progression-free and overall survival were 77% (95% confidence interval, 48%-91%) and 82% (95% confidence interval, 54%-94%), respectively. **Conclusion:** CNS-directed high-dose chemotherapy and ASCT provides durable remission for patients with synchronous aggressive lymphoma and should be strongly considered as consolidative therapy for eligible patients with systemic NHL with CNS involvement in first complete remission.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 17, No. 12, 884-8
Keywords: Blood brain barrier, Chronic lymphocytic leukemia, Diffuse large B-cell lymphoma, High-dose chemotherapy, Mantle cell lymphoma

[1]Department of Medicine, Massachusetts General Hospital, Boston, MA
[2]Memorial University School of Medicine, St John's, Newfoundland, Canada
[3]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA
[4]Center for Leukemia
[5]Blood and Marrow Transplant Program
[6]Center for Lymphoma, Massachusetts General Hospital, Boston, MA
[7]Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, MA
[8]Stephen E. and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital, Boston, MA

Submitted: May 8, 2017; Revised: Jul 19, 2017; Accepted: Aug 7, 2017; Epub: Aug 15, 2017

Address for correspondence: Zachariah DeFilipp, MD, Blood and Marrow Transplant Program, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114
E-mail contact: zdefilipp@mgh.harvard.edu

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2017.08.100

Introduction

Central nervous system (CNS) involvement of systemic non-Hodgkin lymphoma (NHL) is a rare event, occurring in approximately 2% of cases.[1,2] The majority of these occurrences take place at the time of disease relapse.[3] Synchronous CNS involvement at initial diagnosis has historically portended to a poor prognosis in those who undergo standard combination chemotherapy alone, with a median overall survival (OS) of < 6 months.[2-4]

The optimal treatment strategy for synchronous CNS involvement of systemic lymphoma (SCNSL) is uncertain. One area of investigation is the role of autologous stem cell transplantation (ASCT). For patients with CNS involvement at relapse, salvage chemotherapy followed by ASCT has resulted in overall survival at 2 to 5 years of 60% to 90% in small series.[5-8] Given the rarity of SCNSL at diagnosis, treatment strategies vary significantly; however, recent approaches have been modeled after regimens developed for primary CNS lymphoma (PCNSL).[9] Conditioning regimens containing agents that can effectively penetrate the blood brain barrier, such as thiotepa and busulfan, have been associated with promising disease control for relapsed primary and secondary CNS lymphoma.[6-8,10-12] Given the increased risk for relapse with standard therapy alone, we have offered high-dose thiotepa, busulfan, cyclophosphamide (TBC), and ASCT in first remission to such patients. Here, we review our experience with TBC and ASCT in the management of SCNSL in first complete remission (CR1).

Patients and Methods

Data Collection

We performed a retrospective analysis of patients ≥ 18 years of age with a diagnosis of SCNSL at diagnosis who received high-dose TBC and ASCT in CR1. Patients were transplanted at Massachusetts General Hospital or Dana-Farber Cancer Institute/Brigham and Women's Hospital between 2008 and 2016. All patients had a primary diagnosis of NHL. The diagnosis of CNS involvement was made based on CNS imaging, tissue biopsy, or cerebrospinal fluid cytology. We included cases of SCNSL identified and treated within the first treatment course for NHL; cases of SCNSL diagnosed at relapse were excluded. Additionally, patients with PCNSL were excluded from this analysis. All patients were in complete remission, defined as no evidence of tumor on imaging and negative cerebrospinal fluid analysis when available. Patients were identified through institutional transplant databases and clinical data was extracted from individual medical records. Six patients were treated as part of a phase II trial of high-dose thiotepa, busulfan, cyclophosphamide, and high-dose rituximab with autologous stem cell transplantation for patients with CNS involvement by NHL or PCNSL.[11]

ASCT

All patients underwent pretransplant evaluation per institutional standard. The conditioning regimen consisted of intravenous (IV) thiotepa 250 mg/m^2 on days −9, −8, and −7; IV busulfan 0.67 to 0.8 mg/kg every 6 hours on days −6, −5, and −4; and IV cyclophosphamide 60 mg/kg on days −3 and −2. The dosing of busulfan was not pharmacokinetically directed. Additionally, the busulfan dose was reduced to 0.60 mg/kg IV every 6 hours for patients > 60 years of age. Chemotherapy agents were dosed based on ideal or actual body weight, whichever was less. For the patients who received rituximab as part of the phase II trial, rituximab 1000 mg/m^2 was administered on days −9 and −2. Stem cell reinfusion occurred on day 0. Supportive therapy including palifermin, granulocyte colony-stimulating factor, seizure and infection prophylaxis, hydration, and antiemetic therapy and was administered per institutional guidelines.

Statistical Analysis

Patient characteristics were reported descriptively. Neutrophil engraftment date was defined as the first of 2 consecutive days with neutrophil count of at least 0.5 × 10^9/L. Platelet engraftment time was the time from transplant to platelet count greater than or equal to 20 × 10^9/L for 2 consecutive days without transfusion support. Transplant-related toxicities were graded according to the Common Terminology Criteria for Adverse Events. OS was defined as the time from date of transplant to date of death from any cause. Progression-free survival (PFS) was defined as time from date of transplant to date of disease relapse or death from any cause. Relapse was defined as recurrence of lymphoma after a complete response. Patients without progression, relapse, or death from any cause were censored at date of last follow-up. OS and PFS analyses were calculated from the date of ASCT by the Kaplan-Meier method.

Results

Patient Characteristics

Twenty patients with SCNSL at diagnosis who received high-dose TBC and ASCT in CR1 were identified. Clinical characteristics are shown in Table 1. Thirteen patients were male, and 7 were female. The median age at diagnosis was 53 years (range, 37-65 years). Five patients were > 60 years of age. The majority had diffuse large B-cell (DLBCL) histology (n = 17; 85%); other histologic subtypes included chronic lymphocytic leukemia (CLL) (n = 2; 10%) and mantle cell lymphoma (n = 1; 5%). For the patients with DLBCL, molecular subtyping by immunohistochemical expression was available for 13 patients: germinal center B−cell-like, n = 3; non-germinal center B−cell-like, n = 10. Two patients had dual protein expression of MYC and BCL-2. The initial International Prognostic Index risk categories for patients with DLBCL included low (n = 1), low-intermediate (n = 8), high-intermediate (n = 4), and high (n = 4). The 2 patients with CLL had no evidence of the Richter transformation. The site of CNS involvement was parenchymal in 60% (n = 12) and leptomeningeal in 45% (n = 9); 1 patient had concurrent parenchymal and leptomeningeal involvement. Eighteen patients had CNS disease diagnosed prior to beginning therapy. Two patients were diagnosed with CNS disease after the initiation of therapy, at a median of 2 months (range, 1-3 months).

Pretransplant Therapy

All patients underwent initial systemic and CNS-directed chemotherapy. Systemic induction regimens for patients with DLBCL included R-CHOP (rituximab, cyclophosphamide,